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TITLE: Development of a Synthetic Lethal Drug Combination That Targets the Energy Generation Triangle for Liver Cancer Therapy

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14. ABSTRACT Metabolic reprogramming in HCC promotes cancer cell survival and growth. This reprogramming also suggests possibilities to identify as yet unexplored therapeutic targets. While most normal tissues use HK1 for glycolysis, HK4 is the only HK isoform in hepatocytes. The transition from hepatocyte to HCC is frequently accompanied by a complete switch from HK4 to the highly active HK2 isoform, and increased glycolysis (the "Warburg effect"). HK2 gene deletion in adult mice does not significantly affect normal tissues; however, HK2 inhibition in HCC is cytostatic. Our high throughput screen (HTC) discovered diphenyleneiodonium (DPI) as a synthetic lethal partner that, in combination with HK2 inhibition, kills HCC cells through its inhibition of mitochondrial complex I. The combination of HK2 inhibition with DPI shifts fatty acid (FA) metabolism from FA synthesis to FA oxidation (FAO) in HCC cells to compensate energy loss. Compared to normal liver, HCC up-regulates expression of genes involved in FA biosynthesis and down-regulates expression of genes involved in FAO. Perhexiline (PER), a FAO inhibitor in clinical use, sensitizes HCC cells to HK2 inhibition/DPI-induced toxicity. In contrast, the HK2 inhibition/DPI/PER combination does not cause significant cytotoxicity in cells from other cancers (e.g., breast, lung, colon), suggesting this therapy will be tolerated <i>in vivo</i> . In this study, we developed a triple combination of HK2 inhibition, DPI, and PER to target the "energy generation triangle" (glycolysis, oxidative phosphorylation, and FAO) as a translational, effective and safe therapy for HCC.					
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## INTRODUCTION

Despite increasing frequency and lethality rates for hepatocellular carcinoma (HCC, the most common type of liver cancer), sorafenib and its analogue regorafenib remain the only FDA-approved drugs for the management and treatment of patients with advanced disease. However, sorafenib has limited survival benefits with low rates of tumor response, accompanied by frequent adverse effects and development of drug resistance (1). While liver transplantation remains the preferred treatment option for HCC patients, many patients miss their therapeutic windows for liver transplantation, due to the limited management of disease progression and to inadequate availability of liver donors. There is an unmet, urgent need for effective and safe treatments for HCC.

Metabolic reprogramming during hepatocarcinogenesis promotes cancer cell growth and survival, but also suggests the possibility of identifying as yet unexplored drug targets (2). Most cancers, including HCC, increase glycolysis (the “Warburg effect”) to ensure sufficient supplies of energy (ATP), reducing equivalents (NADPH), and biochemical building blocks for cell growth and proliferation (3). Therefore, targeting glycolysis as a potential therapeutic approach has become a major effort in oncology (4). However, because of the conserved nature of the glycolytic pathway in normal tissues, global systemic inhibition of glycolysis results in considerable adverse effects that make this approach of limited value; selective inhibition of cancer glycolysis is required for clinical cancer therapy.

The hexokinase (HK) enzymes, encoded by four genes (HK1/2/3/4), catalyze glucose phosphorylation, the first- and rate-limiting step in glycolysis (5). Most normal tissues, including the brain, use HK1 for glycolysis. HK3 is inhibited by physiological concentrations of glucose. HK4, also known as glucokinase (GCK), is expressed in hepatocytes, pancreas  $\beta$ -cells, and glucose-sensing neurons. HK2 is used primarily by embryonic tissues and by adult muscle and adipose tissues. In addition, HK2 is expressed in most cancers, and was reported to be important, in wide range of cancers, for proliferation in culture and progression *in vivo* (6-9). HK2 gene deletion in adult mice does not significantly affect normal tissues (6), suggesting that specific HK2 inhibition might be a promising therapeutic strategy for cancer treatment. To this end, highly selective HK2 inhibitors have recently been developed (10).

In addition to enhanced glycolysis, other modes of energy generation are utilized to support biological processes in cancer cells; these alternative energy sources include oxidative phosphorylation and fatty acid oxidation (11, 12). The availability and use of multi-source energy generation suggests both the flexibility of cancer cells in reprogramming their energy dependence under metabolic stress and their abilities to escape from energy blockade using monotherapies.

Although multiple studies have reported the important role of HK2 in cancer cell proliferation and tumor progression (6-9), a systematic comparison of the sensitivities of the major cancer types to HK2 silencing has not been described. In addition, a comprehensive search for small molecules synergistic with HK2 knockdown/inhibition for inhibition of cancer has not been reported. We performed a comparison of the effect of HK2 silencing on growth of cancer cells of different origins. Among multiple independently isolated cell culture lines from nine different cancer types, the majority of HCC cells lines expressed HK2, but not HK1, and were by far the most sensitive to cytostasis caused by HK2 silencing by an HK2 shRNA (shHK2). In a high throughput screen (HTS) of 3,205 drug-like compounds, natural products and compounds with a history of clinical trials/use, we identified the mitochondrial complex I inhibitor diphenyleneiodonium (DPI), as the best synthetically lethal partner, in combination with HK2 silencing/inhibition, for HCC cytotoxicity. In addition, suppression of fatty acid oxidation (FAO) by perhexiline (PER), a clinical FAO inhibitor, further sensitized HCC cells to the combination of HK2 silencing/inhibition and mitochondrial complex I inhibition. Triple-combination therapy (shHK2/DPI/PER), targeting energy production in three HK1<sup>-</sup>HK2<sup>+</sup> HCC xenograft models, suppressed tumor growth and was well tolerated by animals. These results warrant optimization of the triple-combination therapy for further clinical development for HK1<sup>-</sup>HK2<sup>+</sup> HCC therapy.

**KEYWORDS:** *hepatocellular carcinoma, glycolysis, hexokinase 2, diphenyleneiodonium, perhexiline, high throughput screen, fatty acid oxidation, electron transport chain, mitochondria complex-I.*

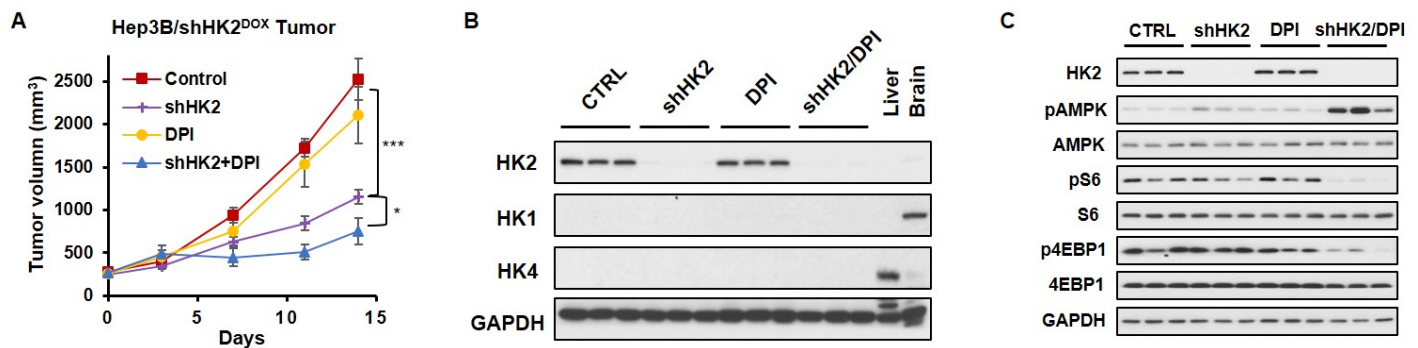
## ACCOMPLISHMENTS

1. The major goals of the project.

The goal of this project is to develop a triple combination of HK2, DPI, and PER inhibition as a translational, effective and safe therapy for hepatocellular carcinoma (HCC).

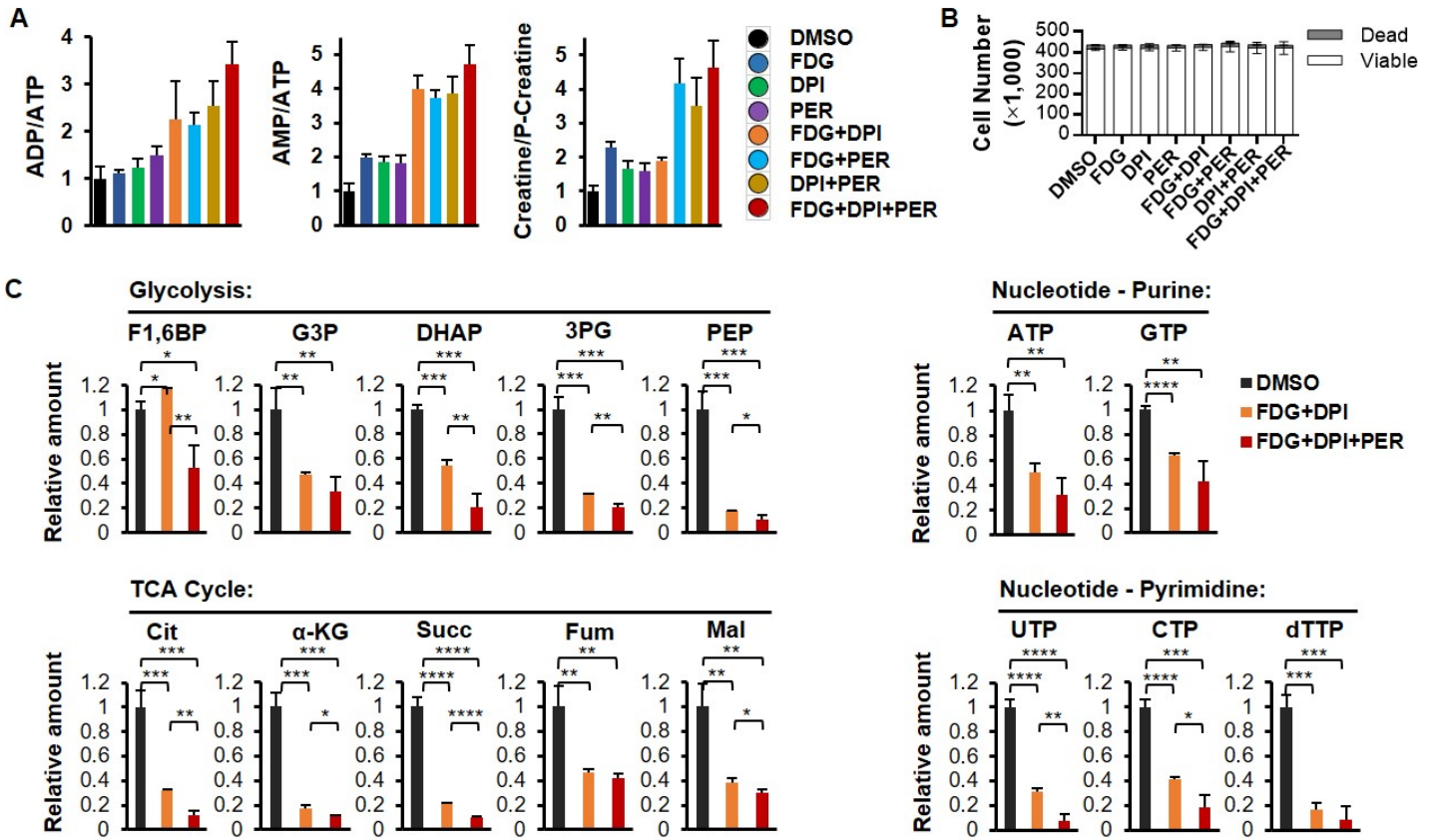
## 2. What was accomplished under these goals?

**2.1. We validated the synthetic lethality of DPI and doxycycline-induced HK2 knockdown in the HCC mouse xenograft model.** Using HCC Hep3B xenograft subcutaneous tumors with stable doxycycline (DOX)-inducible HK2 shRNA (shHK2), we examined the effects of DPI and DOX, both as single agents and in combination. DPI does not have a significant effect on tumor growth, while DOX-induced shHK2 knockdown significantly reduced tumor growth (Fig. 1A). The combination of DPI and DOX-shHK2 resulted in a significant decrease in tumor volume compared to DOX-shHK2 alone, demonstrating a synergistic effect between DPI and shHK2 knockdown in *in vivo* HCC tumors. We confirmed that HCC xenograft tumors did not express other active HK isoforms (HK1 and HK4) to compensate HK2 knockdown (Fig. 1B). In addition, we examined the energy related biomarkers in xenograft tumors, including the energy sensor phospho-AMPK (pAMPK), and the energy-dependent mTOR pathway effectors phospho-S6 (pS6) and phospho-4EBP (p4EBP). The combination of DOX-shHK2 and DPI caused a substantial increase in pAMPK and a decrease both in pS6 and in p4EBP (Fig. 1C). These changes in the energy biomarkers indicate that the DPI/shHK2 combination reduces the HCC cellular ATP level in the tumors.



**Fig. 1. The combination of DPI and shHK2 knockdown is synergistic in xenograft Hep3B/shHK2<sup>DOX</sup> tumors.** (A) DPI enhances the potency of HK2 silencing in Hep3B/shHK2<sup>DOX</sup> tumors. Mice bearing Hep3B/shHK2<sup>DOX</sup> xenografts were given 2 mg/kg DPI (daily i.p.) and/or a DOX-containing diet when tumors reached 200 mm<sup>3</sup> (day 0). (B) Expression of active HK isoforms in xenograft tumors described in panel (A). (C) Effects of HK2 knockdown and/or DPI treatment on AMPK $\alpha$  activation and mTOR pathway inactivation in xenograft Hep3B/shHK2<sup>DOX</sup> tumors described in panel (A).

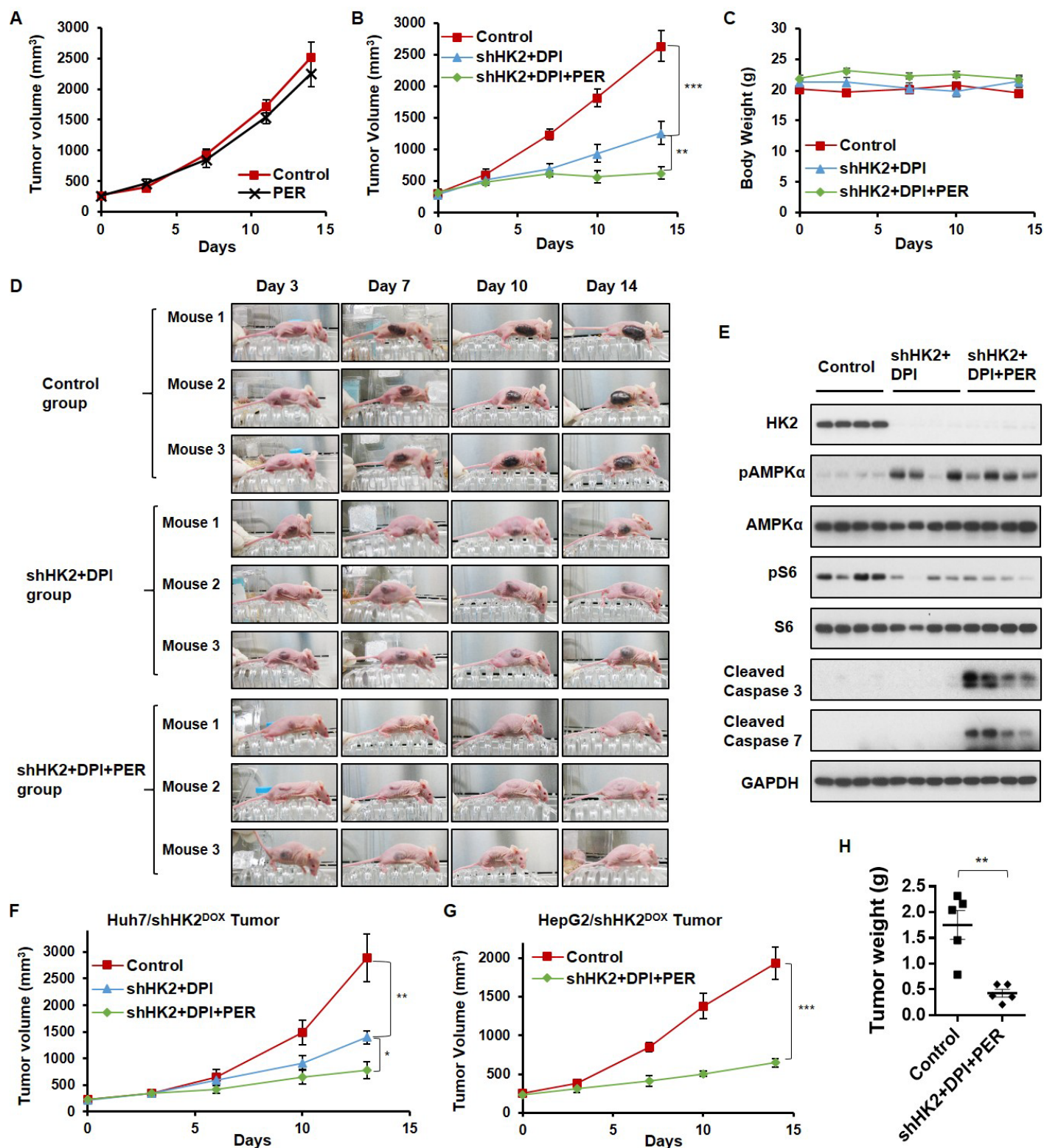
**2.2. We validated the mechanism of action of the triple-combination therapy (shHK2, DPI, PER) that targets the “energy generation triangle”.** Mass spectrometry was used to determine the levels of cellular energy-related molecules extracted from Hep3B cells after an eight-hour treatment with FDG, DPI, and/or PER. The increase in the ADP/ATP and AMP/ATP ratios in response to the triple treatment demonstrated the combined inhibition of ATP production from HK2-mediated glycolysis, oxidative phosphorylation, and FAO (Figure 2A). In addition, the combination of PER with FDG, DPI, or FDG/DPI substantially increased the creatine/P-creatine ratio, limiting the ability of HCC cells to replenish ATP from P-creatine (Figure 2A). These molecular energy changes, as measured by trypan blue exclusion at 8 hours after drug administration, occurred before cell death (Figure 2B). Metabolomics analysis revealed that the pools of most metabolites of glycolysis and the TCA cycle, as well as nucleotide pools, were reduced by FDG/DPI in HK1<sup>-</sup>HK2<sup>+</sup> HCC cells and were further decreased when PER was added into the combination (Figure 2C). These data suggest that global changes in cell metabolism, in association with or caused by energy inhibition, may also contribute to the HK2i/DPI/PER-induced synthetic lethality in HK1<sup>-</sup>HK2<sup>+</sup> HCC cells.



**Fig. 2. Modulation of HCC energy generation and metabolism in Hep3B/shHK2<sup>DOX</sup> cells in response to FDG/DPI/PER treatment.** (A) The HK2i/DPI/PER triple-combination decreases HCC cellular energy levels. After 8 h drug treatment, AMP, ADP, ATP, creatine and P-creatine amounts in Hep3B cells were determined by LC-MS. (B) Hep3B cell count and viability after 8 h treatment with FDG (250  $\mu$ M), DPI (15 nM), and/or PER (5  $\mu$ M). Viability was determined by trypan blue staining. (C) Changes in pool sizes of glycolysis and TCA cycle metabolites, as well as purine and pyrimidine nucleotides after vehicle, FDG/DPI or FDG/DPI/PER treatment in Hep3B cells. F1,6BP, fructose 1,6-biphosphate. G3P, glyceraldehyde 3-phosphate. DHAP, dihydroxyacetone phosphate. 3PG, 3-phospho-glycerate. PEP, phosphoenolpyruvate. Cit, citrate.  $\alpha$ -KG,  $\alpha$ -ketoglutarate. Succ, succinate. Fum, fumarate. Mal, malate. Each data point represents mean  $\pm$  SD of triplicate samples. \*,  $P < 0.05$ . \*\*,  $P < 0.01$ . \*\*\*,  $P < 0.001$ . \*\*\*\*,  $P < 0.0001$ .

2.3. We validated the *in vivo* efficacy of the shHK2/DPI/PER combination in HCC xenograft tumors. We compared, in the same experiment, the efficacy of the triple combination (shHK2/DPI/PER) to the efficacy of the shHK2/DPI double combination in xenograft HCC tumors. In each of the treatment groups, individual Hep3B/shHK2<sup>DOX</sup> mice were switched to the DOX-containing diet when the tumor reached 200 mm<sup>3</sup> (Day 0) to induce HK2 knockdown. DPI and/or PER treatment were started 72 h later (Day 3). While PER alone showed no significant effects on tumor growth (Figure 3A), PER significantly enhanced the potency of the shHK2/DPI combination on Hep3B/shHK2<sup>DOX</sup> HCC tumor progression (Figures 3B and C). No significant change in body weight was detected among the different Hep3B/shHK2<sup>DOX</sup> HCC tumor groups (Figure 3D). While both the shHK2+DPI and the shHK2+DPI+PER treatments activated AMPK $\alpha$  and suppressed the mTOR signaling cascade, only the shHK2+DPI+PER treatment induced the appearance of the apoptosis markers cleaved caspase-3 and cleaved caspase-7 (Figure 3D). These data indicated that, with the reported maximum DPI tolerated dosage and schedule (23), the intratumor amount of DPI was not sufficient to achieve synthetic lethality with HK2 knockdown. However, PER addition sensitized Hep3B cells to the shHK2/DPI combination and induced apoptosis in Hep3B HCC tumors. The potency of the shHK2/DPI/PER combination on HK1<sup>+</sup>HK2<sup>+</sup> HCC tumor growth was also examined with two additional HK1<sup>+</sup>HK2<sup>+</sup> HCC xenografts, Huh7/shHK2<sup>DOX</sup> and HepG2/shHK2<sup>DOX</sup> (Figures 3E, F and G). These results confirm the *in vivo* efficacy and safety of our triple-combination therapy in established-HCC tumors.





**Figure 3. PER sensitizes established xenograft HCC tumors to HK2 knockdown/DPI combination therapy.** (A) PER as a single agent does not have a significantly detectable effect on growth of subcutaneous Hep3B/shHK2<sup>DOX</sup> tumors. After xenograft Hep3B/shHK2<sup>DOX</sup> tumors reached 200 mm<sup>3</sup>, mice were treated with PER (30 mg/kg, daily i.p.) for 15 days. Data are means  $\pm$  SEM. N = 5 mice per group. (B) PER enhances the ability of the HK2 knockdown/DPI combination to retard the progression of Hep3B/shHK2<sup>DOX</sup> tumor xenografts. When tumors reached 200 mm<sup>3</sup> (day 0), xenografts were randomized into a control group and two treatment groups. The control mice were remained on the standard diet and treated with vehicle (n = 7). In the treatment

groups mice were on a DOX-supplemented diet (from Day 0) and treated either with DPI (2 mg/kg, daily i.p. from Day 3, n = 7) or with [DPI (2 mg/kg, daily i.p.)+PER (30 mg/kg, daily i.p.), from Day 3, n = 8]. (C) Representative images of tumor progression in three mice from each group in Panel B. (D) Body weights of the mice in Panel B, bearing xenograft subcutaneous tumors, in response to the indicated treatments. (E) shHK2/DPI/PER treatment activates AMPK $\alpha$ , deactivates S6, and elicits cleavage of caspase-3 and caspase-7. Hep3B/shHK2<sup>DOX</sup> tumors from the indicated treatment groups were collected at day 15. Protein extracts from tissue homogenate supernatants were analyzed. (F) PER enhances the ability of the HK2 knockdown/DPI combination to retard the progression of Huh7shHK2<sup>DOX</sup> HCC tumor xenografts. Experimental conditions are the same as those described in panel A. N = 6. (G) PER enhances the ability of the HK2 knockdown/DPI combination to retard the progression of HepG2/shHK2<sup>DOX</sup> HCC tumor xenografts. Experimental conditions are the same as those described in panel A. N = 5. (H) HK2 knockdown/DPI/PER combination suppresses HepG2/shHK2<sup>DOX</sup> tumor growth. Weights of HepG2/shHK2<sup>DOX</sup> tumors after indicated treatments of the xenografts shown in panel F are shown. All data are expressed as means  $\pm$  SEM. \*, P < 0.05. \*\*, P < 0.01. \*\*\*, P < 0.001.

### 3. What opportunities for training and professional development has the project provided?

The project provided me with training both in the field of cancer cell energy metabolism and in methods for investigating combination therapies in animal xenograft HCC models. In addition, the project supported my attendance in the AACR Synthetic lethality Conference (January, 2017, San Diego), providing me with an important opportunity to learn the frontier research in this area, to present my work to the experts, and to meet many people in this important field of cancer research..

### 4. How were the results disseminated to communities of interest?

The results of this project were presented at the 2017 AACR Synthetic Lethality Conference (January, 2017, San Diego). In addition, I am preparing a manuscript for publication that describes the findings of this study.

### 5. What do you plan to do during the next reporting period to accomplish the goals?

Nothing to report (this is the final report).

## IMPACT

### 1. What was the impact on the development of the principal discipline(s) of the project?

Despite increasing prevalence and lethality for hepatocellular carcinoma (HCC), the need for effective treatment for this disease remains unmet. Unlike most tumors expressing both hexokinase 1 (HK1) and HK2, a subpopulation of HCCs express only HK2 and are highly sensitive to HK2 silencing-induced cytostasis. Diphenyleneiodonium (DPI), a mitochondrial complex-I inhibitor, was identified from a high-throughput screen to be synthetically lethal, in combination with HK2 silencing/inhibition, in HK1<sup>-</sup>HK2<sup>+</sup> HCC cells. Perhexiline, a fatty acid oxidation inhibitor, further sensitizes HCC cells to the complex-I/HK2-targeted combination. Our DoD Horizon Award supported project developed an innovative, effective, and safe therapy for liver cancer treatment. Selective inhibition of the energy generation triangle (glycolysis, oxidative phosphorylation, and fatty acid oxidation), due to the unique presence of only the HK2 isoform, appears promising for the treatment of HK1<sup>-</sup>HK2<sup>+</sup> HCCs. When published, we anticipate that this approach to HCC therapy will be considered for clinical translation.

We have finished three pre-clinical phases in the pathway leading to the clinical application of our proposed therapy: (1) *in vitro* design and discovery of a triple-combination therapy; (2) validation of the molecular mechanism of the proposed drug combination; (3) evaluation of the efficacy and safety of the triple-combination therapy in mouse xenograft models of liver cancer. The achievements in the preclinical evaluation advance our proposed therapy for liver cancer towards the clinical development stage, and bring new hopes for liver cancer



patients. The outcomes of the proposed research should have significant impact on treating the liver cancer patients among active duty service members, the veterans, and their families. The short-term outcomes not only warrant the future clinical studies of the proposed therapy, which has the potential to benefit select liver cancer patients as volunteers participating in the clinical studies, but also become a proof of principle verifying our proposal that targeting the energy generation triangle is an effective and safe strategy to attack liver cancer cells. We anticipate the long-term outcomes of the proposed research to include the FDA approval of this therapy, and the clinical application of this therapy to treat liver cancer patients. Due to the current dearth of effective and safe systematic therapies for liver cancer, liver transplantation remains the preferred option for liver cancer treatment. However, there is a huge gap between the number of liver cancer patients and the number of suitable liver donors. As a result, many liver cancer patients miss the therapeutic window for liver transplantation. Therefore, the long-term outcomes of our proposed research will, we hope, save lives of a large population of liver cancer patients in the military, in veterans, in military families, and in the general population.

## 2. What was the impact on other disciplines?

The achievements and outcomes of our project on HCC also promote the extension of testing this therapeutic strategy – targeting the energy triangle – in other HK1<sup>-</sup>HK2<sup>+</sup> cancer types. As a result, the findings in this DoD-supported project also have potential impacts on patients with other HK1<sup>-</sup>HK2<sup>+</sup> cancers among active duty service members, their families, and other military beneficiaries.

## 3. What was the impact on technology transfer?

Nothing to report.

## 4. What was the impact on society beyond science and technology?

Nothing to report.

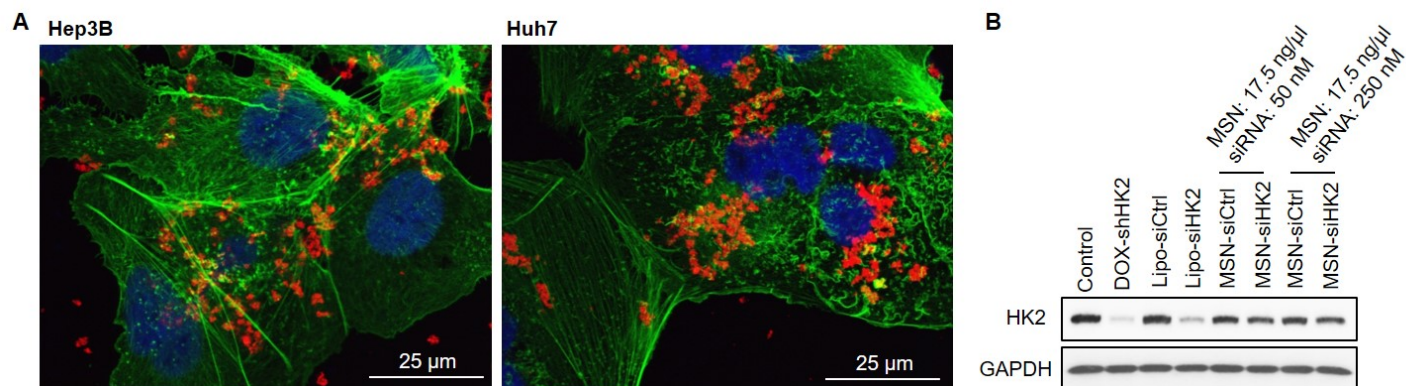
# CHANGES/PROBLEMS

## 1. Changes in approach and reasons for change

Nothing to report.

## 2. Actual or anticipated problems or delays and actions or plans to resolve them.

In the project narrative, we proposed to develop an HCC-targeted mesoporous silica nanoparticles (MSNs) to deliver siHK2 as a translational therapeutic agent (siHK2-MSN), in combination with DPI and PER, to treat HCC. When tested in cell culture, siHK2-MSNs were able to enter HCC cells (Figure 4A). However, siHK2-MSNs do not knockdown HK2 in HCC cells, whereas the same siHK2 sequence delivered by lipofectamine 2000 substantially reduce HK2 protein levels in HCC cells (Figure 4B). We are taking alternative approaches to the development of translational HK2 targeted agents, including small-molecule selective HK2 inhibitors and HK2 specific antisense oligonucleotides (ASOs).



**Figure 4. siHK2-MSNs do not knockdown HK2 in HCC cells.** (A) HCC uptake of optimized MSNs within 1 h. Representative confocal microscopy images are shown. Green: F-actin; Blue: DAPI; Red: Rhodamine B-labeled MSNs. (B) siHK2-MSNs do not knockdown HK2 in Hep3B cells. MSNs were pre-incubated with siRNAs at 4 °C overnight. Dox-induced shHK2 was used as a control, and lipofectamine 2000-mediated siRNAs of the same sequences as the MSN-siRNAs were also included as a control. Cells were collected 72 hr after indicated treatments for Western blotting analysis.

2. Changes that had a significant impact on expenditures.

Nothing to report.

3. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents.

Nothing to report.

4. Significant changes in use or care of vertebrate animals.

Nothing to report.

5. Significant changes in use of biohazards and/or select agents.

Nothing to report.

## PRODUCTS

1. Publications, conference papers, and presentations

Conference presentation: Targeting the energy generation triangle to achieve synthetic lethality for treatment of hepatocellular carcinoma. Conference: Opportunities and Challenges of Exploiting Synthetic Lethality in Cancer (January 2017, San Diego). Abstract number: B37.

## PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

1. What individuals have worked on the project?

Name:	Shili Xu
Project Role:	Principal Investigator

Researcher Identifier (ORCID ID):	0000-0002-4933-8673
Nearest person month worked:	12
Contribution to Project	Dr. Xu has designed the study, and performed all described experiments.
Funding Support:	DoD Horizon Award

2. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report.

3. What other organizations were involved as partners?

Nothing to Report.

### **SPECIAL REPORTING REQUIREMENTS**

Nothing to Report

### **APPENDICES**

None